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Biological indicators of cadmium exposure and toxicity

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Summary. The increasing environmental and occupational exposure of populations to cadmium creates the need for biological indicators of cadmium exposure and toxicity. The advantages and disadvantages of monitoring blood cadmium, urinary, fecal, hair, and tissue cadmium, serum creatinine, β_2-microglobulin, α_1-antitrypsin and other proteins, and urinary amino acids, enzymes, total proteins, glucose, β_2-microglobulin, retinol-binding protein, lysozyme, and metallothionein are discussed. It is concluded that urinary cadmium, metallothionein and β_2-microglubulin may be used together to assess cadmium exposure and toxicity.

Introduction

Cadmium is a heavy metal of increasing prevalence in our environment, due to its industrial production and usage and its emissions from fossil fuel combustion. Specific populations exposed to high levels of cadmium have been studied intensively in order to determine not only the mechanisms of cadmium toxicity, but also biological indicators which can be used to prevent its toxic manifestations by giving an estimate of body burden.

There now exists a great awareness of cadmium's potential health hazard and measures have been taken to reduce the exposure both in the environment and in industry. However, the continuous life-long accumulation of cadmium in the body creates the need for a monitor of body burden and not recent exposure. Also, the severe and possibly irreversible renal tubular dysfunction caused by cadmium necessitates the development of a therapeutic index which is sensitive enough to detect cadmium body burden before irreparable damage is done. Therefore, a search is needed to discover the most sensitive parameters which accurately reflect body burden and also exhibit a measurable change after cadmium exposure.

Many schools of thought exist concerning which parameter would be the best indicator of exposure and of toxicity. A review of the advantages and disadvantages of each one suggested will aid in the development of a rational approach for monitoring cadmium toxicity in susceptible populations. Some of the more commonly used parameters are listed in the table.

Blood cadmium

There is general agreement that although blood cadmium levels do increase with exposure, this increase mainly reflects recent exposure rather than body burden of the metal. Lauwerys et al.[26] showed that blood cadmium correlated with recent exposure in occupationally exposed workers. Also, it was found that blood cadmium reflected recent exposure after an equilibrium was reached at 4 months[28]. Bernard et al.[5] found a similar relationship in rats, in which blood cadmium reached an equilibrium at 3 months, after which it reflected recent exposure. In agreement with this data, blood cadmium was found to be a good indicator of acute exposure to cadmium[3]. Contrary to this evidence, however, Elinder et al.[14] found a signifi-

cant correlation between blood cadmium and hepatic cadmium determined in biopsy material.

Cadmium in urine

The mechanism of urinary excretion of cadmium was studied by Nomiyama et al.[37]. Most cadmium is reabsorbed at the proximal tubules and tubular damage may cause the increased excretion observed. However, pretreatment with urinyl acetate, causing tubular dysfunction, did not subsequently increase the excretion of cadmium, suggesting that the cadmium excretion is not related to renal function.

In the same study Nomiyama et al.[37] also analyzed the relationship between cadmium in urine and in the renal cortex. It was found that urinary cadmium increased with renal cortex cadmium in rabbits that had been given 1.5 mg cadmium/kg/day for up to 5 weeks. This suggests that a close relationship exists between the two. However, they also found a proportional increase in urinary cadmium with plasma cadmium and most data show that cadmium in blood relates more to recent exposure.

In vivo measurement of liver and kidney cadmium and its significance to cadmium in urine was studied by Roels et al.[52]. It was found that the concentration of cadmium in urine followed body burden until this reached levels where renal dysfunction was evident. After this, urinary cadmium increased greatly. It was concluded that the probability of getting renal dysfunction was low when urinary cadmium levels of 10 μg/g creatinine were not regularly exceeded[52]. This supported studies done earlier with animals[5,8,45], showing that cadmium excretion was directly related to dosage, but then increased markedly upon renal damage.

In 2 different studies, Lauwerys et al.[26,28] concluded that cadmium in urine reflected body burden when exposure was low, and recent exposure when exposure was high. This finding was in agreement with the data presented thus far. They postulated that when exposure is high enough to saturate all binding sites, cadmium is excreted in relation to recent exposure. After renal dysfunction, excess cadmium excretion results from 2 sources: from the damaged tubular epithelium, and as a result of decreased reabsorption.

The above data support the use of urinary cadmium as a biological indicator for cadmium exposure in the absence of renal dysfunction. However, contamination of the urine during collection and final analysis makes it difficult to obtain accurate cadmium values. Furthermore, on the basis of cadmium in urine, differences between people with and without renal dysfunction cannot always be found[64], suggesting that cadmium determination in urine should be carried out in combination with other tests.

Parameters used for determining cadmium exposure and renal dysfunction

Parameter	Possible indicator of	References
Blood cadmium	Recent exposure	3, 5, 14, 26, 28
Urinary cadmium	Recent exposure; body burden	5, 8, 26, 28, 37, 45, 52, 64
Fecal cadmium	Dietary intake; recent exposure	17, 25, 56, 58, 65
Hair cadmium	Body burden	3, 10, 16, 29, 42, 44
Tissue cadmium	Body burden	15, 34, 38, 39, 52
Serum creatinine	Glomerular dysfunction	4, 20, 21, 48
Serum β_2-microglobulin	Glomerular dysfunction	4, 20, 21, 48, 66
Serum enzymes	Liver dysfunction	30, 33
Plasma α_1-antitrypsin	Cadmium toxicity	7, 12
Other serum proteins	Liver dysfunction	33, 46, 47, 49
Aminoaciduria	Renal dysfunction	2, 18, 35, 41
Enzymuria	Renal dysfunction	9, 18, 35, 41, 60
Glucosuria	Renal dysfunction	18, 32, 36, 39, 54
Mixed proteinuria	Glomerular and tubular dysfunction	4, 6, 51, 53
Urinary β_2-microglobulin	Tubular dysfunction	1, 4, 21-24, 30, 45, 55, 59, 66
Urinary retinol-binding protein	Tubular dysfunction	30, 31, 33, 39, 40, 50
Urinary lysozyme	Tubular dysfunction	33, 50
Urinary metallothionein	Chronic exposure; body burden; tubular dysfunction	11, 13, 19, 43, 57, 61-64

Cadmium in feces

From a study on the daily excretion of cadmium in normal populations, it was concluded that Japanese adults excrete 25–80 μg cadmium daily in feces. These values agreed with daily cadmium intake via food[65]. Kojima et al.[25] also found that people living in a cadmium-polluted prefecture excreted significantly more cadmium in feces than in control populations; 16.1% of the cadmium-exposed group excreted ≥ 300 μg cadmium/day, while none of the control group excreted this large an amount.

Fecal cadmium has been used as an estimate of daily intake in studying the environmentally exposed people in Japan[25]. The rationale for this practice was derived from evidence that cadmium has low gastrointestinal absorption[17,56] and a low intestinal secretion[17]. However, this method is valid only when the values obtained are used as an estimate of daily dietary intake. Also, large variations in fecal cadmium content probably occur daily. Because of this, it was suggested[25] that data from one day's fecal excretion should be analyzed on a group basis only. Even then, it may not be an accurate indicator of total cadmium exposure (i.e., gastrointestinal, pulmonary and dermal), especially in occupationally exposed populations.

Hair cadmium

Measurement of cadmium in hair has also been suggested as an indicator of body burden. Nordberg and Nishiyama[44] found that hair cadmium correlated well with body burden in mice. Brancato et al.[10] also found a qualitative relationship between hair cadmium and kidney and liver cadmium in rats. It was suggested that it could be used as a biological indicator in the future, however, a quantitative relationship between hair and body cadmium did not exist. Ellis et al.[16] also found a qualitative, but not quantitative, relationship between hair cadmium and body burden in exposed workers.

Another problem exists concerning whether hair cadmium only measures endogenous metal if the expo-

sure is from the air. Significant amounts of cadmium have been shown to adsorb to hair, with individual variability, based on hair acidity[29].
Reviewing diagnostic procedures for subacute cadmium toxicity in jewelry workers, hair was considered a poor indicator because of extrinsic contamination with cadmium[3]. The inability to remove the extrinsic cadmium by washes could have been due to its adsorption and incorporation into the hair's protein matrix by binding to sulfhydryl groups. The possibility of using hair cadmium cannot be ruled out completely, however, since under conditions of solely oral intake of cadmium, it may very well reflect body burden[42].

Tissue cadmium

The introduction of a mobile facility for determining tissue metal levels by in vivo neutron activation provides a significant and unique contribution to the field of heavy metal toxicology[52]. There now exists a means of measuring cadmium in the kidney and liver of exposed individuals. Recent studies using this technique have proposed new critical concentrations of cadmium in the human renal cortex. In cadmium smelter workers, 300–400 μg/g renal cortex was designated as a critical concentration above which renal dysfunction may occur[15]. However, Roels et al.[52] suggest a lower range of critical cadmium concentration in the renal cortex of 160–285 μg/g, beyond which a high percentage of the subjects develop renal dysfunction.
Nomiyama[34] suggests a possible critical cadmium concentration of > 300 μg/g wet weight based on animal data. In rhesus monkeys exposed to cadmium through the diet, the critical concentration was estimated as 380 μg/g for the appearance of low molecular weight proteinuria, and 450 μg/g for proteinuria, glucosuria and amino acid uria[39].
The use of measuring cadmium solely in the renal cortex has questionable value, however. Roels et al.[52] found that the cadmium concentration is higher in the renal cortex of exposed individuals who still have normal renal function. This is in agreement with data on monkeys[38] which showed a decrease in renal cortex cadmium with the appearance of protein and glucose in the urine.
Therefore, renal cadmium alone is not an acceptable indicator of cadmium exposure or toxicity, and other parameters would have to be examined concomitantly. Furthermore, in humans, due to the potential radiation hazard of the neutron activation analysis, the procedure has limited usefulness in monitoring the same population routinely.

Serum β_2-microglobulin and creatinine

Serum β_2-microglobulin and creatinine, which exhibit changes in concentration with cadmium exposure, have been suggested as biological indicators. For example, in cadmium-exposed workers, serum β_2-microglobulin increases along with an increase in blood cadmium[48,66]. This increase is independent of serum creatinine and occurs in the presence of normal creatinine values[48]. This suggests that it may be a result of increased synthesis of β_2-microglobulin in addition to decreased glomerular filtration rate. This parameter may, then, give false positive results if used for testing glomerular function. Therefore, serum creatinine, which rises when glomerular filtration decreases, is probably a better estimate of glomerular function in exposed people. Knowledge of glomerular status is relevant because several studies from Belgium indicate that cadmium causes both glomerular and tubular damage[4,27,53]. This will be discussed in greater depth when reviewing urinary parameters. Another study on occupationally exposed workers found no changes in serum β_2-microglobulin even with high β_2-microglobulin in urine. Thus, they concluded that it was not a good indicator of toxicity[20].
In conclusion, increased serum creatinine or β_2-microglobulin are non-specific indicators of glomerular function, with secondary effects also causing increases in serum β_2-microglobulin. Alone they cannot be used as a monitor of cadmium toxicity, unless it is well established that no other disease state is present[21].

Serum enzymes

In studying chronic cadmium poisoning manifested as Itai-Itai disease, high blood levels of glutamic oxaloacetic transaminase, alkaline phosphatase and lactate dehydrogenase were observed[33]. These data are representative of an advanced picture of cadmium poisoning, however, and studies which show the most sensitive of these enzymes have yet to be done.
When comparing these to urinary values, high alkaline phosphatase and low phosphorus in serum correlate significantly with proteinuria or combined proteinuria and glucosuria in inhabitants of an Itai-Itai endemic district[30]. Also, the prevalence rates of these indices rise proportionately with increasing cadmium concentrations in urine. Therefore, the possibility exists that serum alkaline phosphatase and phosphorus levels could give an indication of cadmium induced renal toxicity.

Serum α_1-antitrypsin

Finally, there has been an interest in monitoring α_1-antitrypsin levels in plasma as a biological indicator of cadmium toxicity. One study shows a dose-dependent decrease in α_1-antitrypsin and its respective trypsin inhibitory capacity in human plasma in vitro, with cadmium administration[12]. This finding caused Bernard et al.[7] to measure plasma α_1-antitrypsin levels in cadmium-exposed workers. However, in this population, they did not find a significant change in antitrypsin levels.

Other serum proteins

Piscator studied the electrophoretic patterns of both urinary and serum proteins extensively[46,47]. In one study, cadmium-exposed workers were found to have a significantly higher γ-globulin fraction, causing a statistical difference in total protein content between control and exposed workers. Similarly, total hexose and seromucoid hexose contents were significantly

different between the two groups[46]. However, a later study, also done on cadmium-exposed workers, gave generally normal results in the exposed group, with increases in α- and γ-globulins in some cases[47].
Piscator and Axelsson[49] then studied serum proteins in rabbits, 7 months after a 6-month exposure to cadmium. There was no difference found between those rabbits which were exposed and the controls. This suggests that liver function normalized in the exposed rabbits, even though much greater hepatic cadmium concentrations were found. This evidence indicates that a) serum proteins are not good indicators of cadmium body burden, and b) large amounts of cadmium can be tolerated in the kidney and liver without developing pathological abnormalities.
Lastly, total protein content in serum has been shown to decrease in patients with Itai-Itai disease[33]. Whether this is an effect of advanced renal damage is unknown.

Amino aciduria

There are opposing reports regarding the value of using amino aciduria as an indicator of cadmium toxicity. Nomiyama[35,41] found that it was one of the earliest signs of cadmium toxicity in rabbits, having appeared in the urine after 16 weeks of exposure, whereas proteinuria and glucosuria occurred after 27 weeks. However, Axelsson and Piscator[2] found that amino aciduria occurred later than proteinuria and glucosuria in cadmium-exposed workers. Similarly, amino aciduria in Japanese workers in lead and cadmium industries was found to be a less sensitive parameter than proteinuria[18]. In summary, there is still some question about the validity of amino aciduria as a sensitive indicator of cadmium exposure.

Enzymuria

There is more agreement that enzymuria may be indicative of renal damage, especially if particular interest is given to where the enzymes originate from, and, therefore, where the damage has been done.
In analyzing the effects of dietary cadmium (300 ppm for 54 weeks) on rabbits, Nomiyama[35,41] found that, in addition to amino aciduria, enzymuria was one of the earliest signs of toxicity. While enzymes (alkaline phosphatase, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase) appeared in the urine after 16–28 weeks of exposure, protein and glucosuria were observed only after 27 weeks. Enzyme clearance studies also showed that acid phosphatase, alkaline phosphatase, glutamic oxaloacetic transaminase, and glutamic pyruvic transaminase were of renal rather than serum origin. However, in this study, acid phosphatase levels were independent of alkaline phosphatase, even though both originate from the proximal tubules.
Two-phase increases in alkaline phosphatase were also seen in rats after parenteral administration of cadmium. An initial increase was seen within 48 h, and was followed by a persistent enzymuria after 15 days[9]. This is further evidence for the use of alkaline phosphatase in urine as a non-specific indicator of renal damage.
Other specific enzymes have been observed which increase in urine with cadmium exposure. Specifically, carbonic anhydrase C increases in urine 10–250 times in cadmium-exposed workers compared to normal subjects[60]. This is particularly relevant since this enzyme originates from damaged tubular cells.
In summary, enzymuria is a possible indicator for non-specific renal damage. However, the absence of any other possible disease state must be assured before renal damage in a clinical setting can be recognized as a result of cadmium toxicity. Yet, the observation that general enzymuria occurs before changes in tubular function or glomerular filtration rate[35,41] suggests that this parameter may be indicative of very early renal dysfunction. This gives it potential value as an index of function which reflects renal status before the development of nephropathy. Further work, however, is needed to identify the most suitable enzyme to be analyzed.

Glucosuria

Glucosuria has been observed in cadmium-exposed animals[39,54], cadmium workers[54], and inhabitants of cadmium-polluted areas[32]. After subcutaneous administration of cadmium in rabbits, the critical concentration of cadmium in the renal cortex was observed to be 120 µg/g for the appearance of glucosuria[36]. Using oral administration of cadmium in rabbits, however, Nomiyama found 300 µg/g to be the critical concentration at which glucosuria develops[36]. In other studies on rabbits and monkeys, Nomiyama[18,39] observed that glucosuria was indicative of a later stage in cadmium toxicity than low molecular weight proteinuria. It is generally not considered an early sign of renal effects of cadmium in exposed populations, and therefore would only be a biological indicator of advanced cadmium toxicity.

Mixed proteinuria

Proteinuria gives great insight into the nature of the dysfunction present. The excretion of low molecular weight proteins in the urine reflects a problem with tubular reabsorption, while high molecular weight proteins in urine reflect problems with glomerular filtration. Although classically cadmium is thought to cause only proximal tubular damage, there is evidence that glomerular damage also occurs. Bernard et al.[4] found, in exposed workers, increased high molecular weight proteins (orosomucoid, immunoglobulin G, albumin, transferrin) in the urine, and a decreased creatinine clearance. This, in addition to increased serum creatinine and β_2-microglobulin, suggests glomerular impairment. There is even evidence that glomerular dysfunction may precede classical tubulopathy since workers with less than 20 years exposure showed only high molecular weight proteinuria, and workers with more than 20 years exposure showed a mixed proteinuria[53]. This theory is confirmed in cadmium-exposed rats which developed a similar mixed proteinuria and not just low molecular weight pro-

teinuria[6]. However, Roels et al.[51] concluded that low molecular weight proteinuria, especially β_2-microglobulinuria, is more sensitive for cadmium toxicity than high molecular weight proteinuria because increases of β_2-microglobulin are significantly higher than increases in albumin at a urine cadmium concentration of 10 µg/g creatinine. Also, since their excretion takes place by 2 separate mechanisms, conclusions cannot be made that one systematically occurs before the other.

β_2-Microglobulin in urine

The significance of low molecular weight proteinuria, particularly β_2-microglobulinuria, has been studied extensively. The level of this protein in urine was shown to increase in long term cadmium exposure in mice[45] and also in environmentally or occupationally exposed populations[4,30,55,59,66]. This low molecular weight proteinuria was much higher (100–300×) than total proteinuria (7–17×) in Itai-Itai patients, and was, therefore, considered a more sensitive indicator[59]. β_2-Microglobulin values greater than 280 µg/g were not found in occupationally exposed workers until after 4 years of exposure. Similarly, in another group of exposed workers values greater than 1000 µg/l were not found unless 10 years or more of exposure had occurred[1]. Therefore, duration, and not intensity, of exposure appears to be important. The correlation between years of exposure to cadmium and urinary β_2-microglobulin was reinforced by various studies[4,22,24]. Tsuchiya[66] found that β_2-microglobulin in urine closely correlated with age, again indicating an association with the duration of cadmium exposure, since cadmium accumulates with age. He also postulates that increased urinary β_2-microglobulin could be due to increased serum β_2-microglobulin. Furthermore, the levels of the protein in serum correlated with cadmium levels in blood, suggesting the possibility that cadmium stimulates its synthesis. He concluded that it is difficult to assume that increased urinary β_2-microglobulin is solely an effect of tubular dysfunction.

Kazantzis[21] suggested that urinary β_2-microglobulin be used for cumulative cadmium exposure and not short-term exposure, indicating that it does reflect body burden and toxicity. Kjellström and Piscator[23], however, reasoned that cadmium-induced tubular damage has progressed severely when β_2-microglobulin increases in the urine, and using it as an indicator would only serve to determine that irreversible damage has occurred.

In conclusion, most evidence supports the use of urinary β_2-microglobulin as an indicator of renal dysfunction. Yet, the possibility does exist that increased synthesis of the protein causes increased levels in blood and subsequent increases in urine. Also, it should be pointed out that the ability of other disease states (i.e., congenital Fanconi syndrome, chronic pyelonephritis, upper urinary tract infection, etc.) to increase urinary β_2-microglobulin levels, makes it a non-specific indicator, more related to renal function than cadmium exposure.

Retinol-binding protein and lysozyme in urine

Various low molecular weight proteins, besides β_2-microglobulin, are excreted in the urine after cadmium exposure. Retinol-binding protein appears to be the most evident and increases in its excretion are seen in exposed animals[39] and cadmium-exposed populations in Japan[30,31,33,40].

Nomiyama[39] found that the highest exposure group of rhesus monkeys (300 ppm, diet) excreted increased retinol-binding protein after 12 weeks and increased protein, glucose, and amino acids in urine only after 16 weeks. Nogawa et al.[30,31,33] used urinary retinol-binding protein as one of the indices of renal effects of cadmium in various Japanese studies and reported that the retinol-binding protein increased significantly in urine along with other low molecular weight proteins.

The excretion of this protein is commonly thought to be a result of decreased tubular reabsorption[50]. This is also true in the case of lysozyme, another protein which has been shown to increase in urine with chronic cadmium poisoning[33]. Both of these, however, are non-specific indices of renal function and are not directly related to cadmium. Furthermore, among all substances used as indices of renal damage, β_2-microglobulin in urine showed the highest prevalence rate for both men and women environmentally exposed to cadmium[30]. For this reason, β_2-microglobulin may be a better low molecular weight protein to measure in urine as a non-specific indicator of renal function.

Metallothionein in urine

Metallothionein is a low molecular weight protein which is induced by cadmium[13] and which binds cadmium ions[19]. Small amounts of metallothionein are detected in plasma after cadmium exposure[61]. It is also shown that metallothionein is filtered and reabsorbed by the kidney. Its relationship with cadmium and renal function makes it potentially ideal to study cadmium's effect on the kidney.

In both occupationally and environmentally exposed people, metallothionein excretion increases[62–64] and appears to be related to cadmium concentrations in the kidney and liver[62]. Such a relationship in cadmium-exposed workers was shown when cadmium was measured by in vivo neutron activation analysis[15] and metallothionein by a radioimmunoassay[61]. The logarithm of urinary metallothionein concentration of the workers showed a linear relationship with the logarithm of the liver cadmium concentration. Similarly, in workers which had normal renal function, cadmium in the kidney showed a significant correlation with urinary metallothionein[62] (fig. 1). Studies in rats support this observation[62]. One difference found, however, was the appearance of a critical concentration of cadmium in rat kidney and liver. Once this threshold was reached, urinary metallothionein increased greatly.

When analyzing metallothionein as a potential index of renal dysfunction in environmentally and occupationally exposed populations, a significant correlation between metallothionein in urine and cadmium in

urine was found[57,64] (fig. 2). Furthermore, it was possible to separate the cadmium-exposed population into groups of normal or abnormal renal function on the basis of urinary metallothionein values. This suggests that metallothionein not only has a definitive relationship with cadmium, but also with renal function.

The relationship between urinary cadmium and urinary metallothionein was also observed by Chang et al.[11] in cadmium-exposed workers. They suggest that metallothionein in urine is more related to cadmium exposure than renal function because no difference was found in subjects with and without renal dysfunction in this study.

Nordberg et al.[43] suggest that because β_2-microglobulin and metallothionein in urine are not always directly related in cadmium-exposed workers (the highest β_2-microglobulin corresponded to the lowest metallothionein value), the type of information derived from both may be different. This is in agreement with the view that β_2-microglobulin is a better indicator of general, non-specific renal status, and metallothionein a better indicator of cadmium body burden.

In summary, although metallothionein is also induced by other heavy metals, and not just by cadmium, it correlates well with the body burden of cadmium.

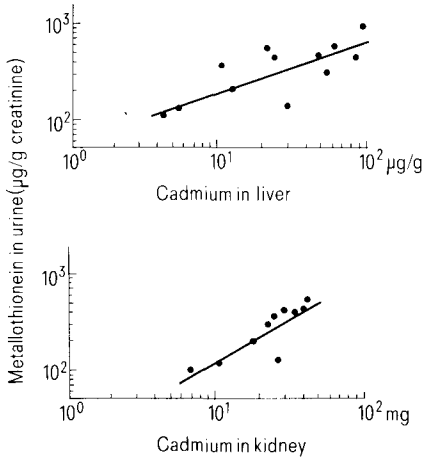

Figure 1. The relationship of metallothionein in urine to cadmium in liver ($r = 0.75$, $p < 0.01$) and in left kidney ($r = 0.85$, $p < 0.01$) of cadmium smelter workers. Modified from Tohyama et al.[62].

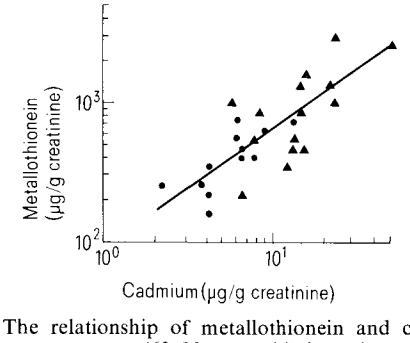

Figure 2. The relationship of metallothionein and cadmium in urine of Japanese women (60–90 years old) from the cadmium-polluted (▲) and non-polluted (●) areas ($r = 0.80$, $p < 0.001$). Adapted from Tohyama et al.[64].

This, in addition to its correlation with cadmium in urine, suggests that it is a good indicator of cadmium exposure. Because the subjects with and without renal dysfunction can be separated by urinary metallothionein and β_2-microglobulin values, and not by cadmium in urine[64], the former two parameters may be more sensitive for determining cadmium-induced renal damage.

Conclusion

Although there are many parameters suggested for use as potential biological indicators for cadmium toxicity, none appears to be suitable by itself. Based on the existing knowledge, the measurement of urinary cadmium, metallothionein, and β_2-microglobulin appears to be the most rational strategy to use in detecting and monitoring cadmium toxicity.

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Cadmium contamination in agriculture and zootechnology

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Introduction

Fortunately, acute Cd toxicity caused by food consumption is rare, but chronic exposure to significant Cd levels in food (and specially in plant materials) may be more frequent. It could significantly increase the accumulation of this heavy metal in certain body organs of man or animals (kidney, liver, etc.).

For populations not exposed to Cd from fall out or to professional contamination, the main source of Cd body burden is also from food. The Food and Drug Administration reported an average daily ingestion of 39 µg/day for 15-20-year old males in the USA[44].

Drinking water and ambient air contribute relatively little to the daily intake. Cigarette smoking is another risk for Cd intake by inhalation. Occurrence of Cd in the food chain and in tobacco is certainly the main source for human or animal contamination.

The concentration of Cd in foods is controlled by its level in the soil, its availability for plants, and by the physical and chemical properties of the growing substrate.

Some agricultural practices, as phosphatic fertilizers, sewage sludge disposal, town-refuse composts applications etc., may increase Cd accumulation in soil and lead to heavy metal transfer to crops and to the food chain.

1. *Cd additions to the soil through environmental pollution and agricultural practices*

The concentration of Cd in most soils is in the range of 0.5-1.0 mg/kg, although concentrations above 20 mg/kg occur naturally in some mining areas. Following Davies and Roberts[11] we may consider that concentrations of Cd, in agricultural soil, in excess of 2.4 mg/kg are anomalously high. Raised concentrations of Cd in soil may be found naturally or as a result of pollution from mining or smelting (e.g. in the Meuse Valley[14,15,45]) or from moving sources (principally automobiles).

The dispersal of metal rich waste around mine and smelting plants has led to high concentrations of Cd in top soils at various localities (e.g. La Calamine, Plombières, Engis, in Belgium). Atmospheric fall-out raise levels of Cd in industrial and urban areas, even in rural areas. Secondary metal refining activities, waste incineration, tyre and oils residues from vehicles, also dissipate Cd into the environment[12].

Agricultural soils are mainly contamined by phosphatic fertilizers and sludge disposal. The Cd content of rock phosphate is variable and depends on its geographical origin[70]. In a Belgian survey of 31 common phosphatic fertilizers Beaufays and Nangniot[6] found Cd concentrations ranging from 0.1 to 80.8 mg/kg. In glasshouses, where intensive cultures of vegetables are performed, an excess of phosphatic fertilizers presents an important hazard of Cd pollution, especially when leafy vegetables (lettuce, spinach etc.) are grown. Andersson[3] calculated that if the Cd concentration in phosphatic fertilizers exceeds 8 mg/kg, Cd levels in top soil may be increased.

The use of Cd-containing agricultural sprays (plant protection chemicals containing Cd are rare) or soil amendments is limited to phosphatic fertilizers or micro nutrients solutions.

In flooded rice culture, as practiced in the Po Valley, the irrigation water is the most important vector of the heavy metals Cd, Cu and Cr. The maximum yearly